Alcohol-induced suppression of KDM6B dysregulates the mineralization potential in dental pulp stem cells.

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Public Summary:
Hallmark features of fetal alcohol syndrome include decreased mineral (calcium) deposition into teeth and bones. Our results suggest that alcohol inhibits the expression of genes involved in depositing calcium into bones and teeth, and that adult dental pulp stem cells are able to reverse the damaging effects of alcohol on this process.

Scientific Abstract:
Epigenetic changes, such as alteration of DNA methylation patterns, have been proposed as a molecular mechanism underlying the effect of alcohol on the maintenance of adult stem cells. We have performed genome-wide gene expression microarray and DNA methylome analysis to identify molecular alterations via DNA methylation changes associated with exposure of human dental pulp stem cells (DPSCs) to ethanol (EtOH). By combined analysis of the gene expression and DNA methylation, we have found a significant number of genes that are potentially regulated by EtOH-induced DNA methylation. As a focused approach, we have also performed a pathway-focused RT-PCR array analysis to examine potential molecular effects of EtOH on genes involved in epigenetic chromatin modification enzymes, fibroblastic markers, and stress and toxicity pathways in DPSCs. We have identified and verified that lysine specific demethylase 6B (KDM6B) was significantly dysregulated in DPSCs upon EtOH exposure. EtOH treatment during odontogenic/osteogenic differentiation of DPSCs suppressed the induction of KDM6B with alterations in the expression of differentiation markers. Knockdown of KDM6B resulted in a marked decrease in mineralization from implanted DPSCs in vivo. Furthermore, an ectopic expression of KDM6B in EtOH-treated DPSCs restored the expression of differentiation-related genes. Our study has demonstrated that EtOH-induced inhibition of KDM6B plays a role in the dysregulation of odontogenic/osteogenic differentiation in the DPSC model. This suggests a potential molecular mechanism for cellular insults of heavy alcohol consumption that can lead to decreased mineral deposition potentially associated with abnormalities in dental development and also osteopenia/osteoporosis, hallmark features of fetal alcohol spectrum disorders.